



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/DK94/00310 <b>(22) International Filing Date:</b> 19 August 1994 (19.08.94) <b>(30) Priority Data:</b> 0950/93                      20 August 1993 (20.08.93)                      DK <b>(71) Applicant (for all designated States except US):</b> NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GRAM, Karen, Susanne [DK/DK]; Skovbrynet 4, DK-2880 Bagsvaerd (DK). JENSEN, Annelise [DK/DK]; Aprilvej 15, DK-2730 Herlev (DK). <b>(74) Common Representative:</b> NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsvaerd (DK).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> A NOVEL PHARMACEUTICAL FOR ORAL ADMINISTRATION COMPRISING PROGESTERONE AND A POLYETHYLENE GLYCOL TOGETHER WITH AN EXCIPIENT  <b>(57) Abstract</b>  A pharmaceutical composition for oral administration of progesterone may, conveniently, contain a PEG, and a further excipient selected from the group comprising a starch, a cellulose, pecting, and tragacanth.		

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A novel pharmaceutical for oral administration comprising progesterone and a polyethylene glycol together with an excipient

#### FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition in the form of a dosage unit for oral administration of progesterone or of progesterone and estradiol.

#### BACKGROUND OF THE INVENTION

Progesterone is a steroid hormone secreted by the ovaries in mammals. Its major biologic functions are to prepare the uterine endometrium for fertilization and implantation of a fertilized ovum and to support pregnancy. Also, when no conception occurs, progesterone plays an important role in the maturation of the uterine endometrium which precedes the shedding of the epithelial layer thereof during the menstrual bleeding.

The amount of progesterone secreted per day by women varies during the menstrual cycle. Thus, during the follicular phase about 1 - 2 mg per day is secreted resulting in a serum level of approximately 0.1 - 1.5 ng/ml. During the luteal phase about 10 - 20 mg per day is secreted resulting in a serum level of approximately 5.7 - 28.1 ng/ml. In the advanced stages of pregnancy, the secretion of progesterone rises to several hundred mg per day.

Progesterone deficiency in women may i.a. lead to dysfunctional uterine bleeding, amenorrhea, endometrial hyperplasia and carcinoma, premenstrual tension and endometriosis.

Immediately, the most obvious way to solve the problems related to progesterone deficiency would seem to be to administer progesterone to allow for the deficiency. However, when administered orally, non-micronized progesterone is gen-

erally found to have a low bioavailability. This fact together with the fact that the first-pass liver metabolism of progesterone is very high has hitherto made oral administration of progesterone problematic. Rectal or vaginal  
5 suppositories provide modest levels of progesterone, but are esthetically displeasing to many women. Progesterone may also be administered by intramuscular injection. However, besides being painful, this route of administration is inconvenient because it is unsuited for self-care by the patient.

10 As a substitute for progesterone, a number of synthetic progestogens have been used in hormone replacement therapy for treating conditions resulting from progesterone deficiency and in oral contraceptives. Such synthetic agents can be tailored to have the desired properties as regards their ab-  
15 sorption and excretion. Although the biologic effects of some of these agents are very similar to the biologic effects of progesterone they are not identical and adverse reactions are well recognised. Thus, certain synthetic progestational agents possess an androgenic effect with a long term risk of  
20 virilisation and a risk of masculinisation of the foetus in the case of treatment during pregnancy. Other derivatives have a long term estrogenic effect. Contrary to progesterone, some of the synthetic progestational agents have no anti-estrogenic effect, anti-aldosteronic effect or anti-ovulatory  
25 effect.

US patents Nos. 5,116,619 and 5,084,277 (Greco et al.) describe a vaginal progesterone tablet and a method of making the same tablet, respectively. One of the stated objects of said invention is to provide a vaginal tablet having a pro-  
30 longed bioavailability. In the description, it is mentioned that the optimization of disintegration times for vaginal tablets is quite different from more traditional theoretical and practical approaches that are utilized for oral dosage forms. An important point, it is stated, is the choice of  
35 disintegrant. The differing amounts of moisture present in

the mouth and in the vagina are primarily responsible for the different approaches required in these two regions. If large amounts of "super disintegrants" suitable in tablets for oral administration are used in vaginal tablets they may, after vaginal insertion, form a sponge-like mass. Smaller amounts of super disintegrants may cause the formation of a gelatinous sheath around the tablet. In both cases, the bioavailability is reduced. These problems with vaginal tablets are overcome by using a starch disintegrant. According to the Greco et al. patents, the optimum formulation for a vaginal tablet contains about 7% of corn starch. The patents contain no disclosure as to whether starch would have a favourable influence on the bioavailability of progesterone after oral administration.

US patent No. 4,196,188 (Besins) discloses an orally administerable form of progesterone which is administered in a soft gelatine capsule containing an oil vehicle. Micronized progesterone crystallized and milled in a very specific way is used in the preparation of the capsules. It is stated that such micronized progesterone is unsuited for manufacturing compressed dosage forms such as tablets, since the tableting process influences the particle size distribution in an unfavourable manner.

British patent application No. 2,091,552 (Carnrick) discloses a unit dosage of progesterone in conjunction with a suitable pharmaceutical carrier which may be cholesterol pivalate. No further details of the composition are given.

One object of the present invention is to provide a pharmaceutical composition in the form of a dosage unit for oral administration of progesterone which composition has a favourable bioavailability.

Another object of the present invention is to provide a pharmaceutical composition in the form of a dosage unit for oral

administration which is suitable for treating progesterone deficiency conditions.

It is a further object of the present invention to provide a pharmaceutical composition in the form of a dosage unit for oral administration which dosage unit comprises progesterone and estradiol.

It is a further object of the present invention to provide a pharmaceutical composition for oral administration of progesterone in which the weight of the progesterone constitutes a high percentage of the total weight of the tablet.

It is a still further object of the present invention to provide a method of making a pharmaceutical composition of progesterone, optionally also containing estradiol, for oral administration having an improved bioavailability of the progesterone.

#### SUMMARY OF THE INVENTION

Surprisingly, it has turned out that a polyethylene glycol together with an excipient selected from the group comprising a starch, a starch component, a modified starch, a cellulose, a modified cellulose, pectin, and tragacanth has a favourable influence on the bioavailability of progesterone in dosage units for oral administration.

Accordingly, in its broadest aspect, the present invention relates to a pharmaceutical composition in the form of a dosage unit for oral administration which composition comprises progesterone and a polyethylene glycol together with an excipient selected from the group comprising a starch, a starch component, a modified starch, a cellulose, a modified cellulose, pectin, and tragacanth.

According to one preferred embodiment of the invention, the progesterone contained in the dosage unit is micronized.

According to another preferred embodiment of the invention, the composition further comprises estradiol.

5 According to another preferred embodiment of the invention, the amount of progesterone contained in each dosage unit is in the range of from about 10 mg to about 500 mg, more preferred from about 20 mg to about 300 mg, most preferred from about 50 mg to about 225 mg.

10 According to another preferred embodiment of the invention, the amount of estradiol contained in each dosage unit is in the range of from about 0.1 mg to about 5.0 mg, more preferred from about 0.4 mg to about 2.0 mg.

According to another preferred embodiment of the invention,  
15 the composition comprises a polyethylene glycol having an average molecular weight in the range of from about 1000 to about 10,000.

According to another preferred embodiment of the invention, the composition comprises a polyethylene glycol having an  
20 average molecular weight of about 6000.

According to another preferred embodiment of the invention, the composition comprises starch in the form of maize starch.

According to another preferred embodiment of the invention, the composition comprises starch in the form of potato  
25 starch.

According to another preferred embodiment of the invention, the composition comprises starch in the form of rice starch.

According to another preferred embodiment of the invention, the composition comprises starch in the form of wheat starch.

According to another preferred embodiment of the invention, the composition comprises starch in the form of tapioca  
5 starch.

According to another preferred embodiment of the invention, the composition comprises a modified starch.

According to another preferred embodiment of the invention, the composition comprises a starch component in the form of  
10 amylose.

According to another preferred embodiment of the invention, the composition comprises a starch component in the form of amylopectin.

According to another preferred embodiment of the invention,  
15 the amount of starch contained in the dosage unit constitutes from about 5% to about 75% by weight, more preferred from about 15% to about 50% by weight, most preferred from about 21% to about 30% by weight of the dosage unit.

According to another preferred embodiment of the invention,  
20 the amount of progesterone contained in the dosage unit constitutes at least about 25%, more preferred at least 33% of the total weight of the dosage unit.

According to another preferred embodiment of the invention, the composition is provided in the form of a dosage unit con-  
25 taining an amount of progesterone or of progesterone and estradiol which is appropriate to cover either the full daily need of a person to be treated or a simple fraction thereof such as one half or one third of the full daily need. Most preferred is a dosage unit containing the full daily need.



**DETAILED DESCRIPTION OF THE INVENTION**

Progesterone can exist in two crystal modifications of equal physiologic activity and which are easily interconverted. As used in the present description, the designation progesterone comprehends both forms. In many references, progesterone is referred to as "natural progesterone". In the present description, the designation progesterone comprehends progesterone of any origin, be it isolated from biologic material, synthetic, or semisynthetic. Progesterone can also be designated pregn-4-ene-3,20-dione.

The progesterone used in the compositions of the present invention is micronized. It is preferred that at least about 90% of the particles have a diameter less than 15  $\mu\text{m}$ , that about 50% of the particles have a diameter less than 10  $\mu\text{m}$ , and that about 10% of the particles have a diameter less than 5  $\mu\text{m}$ .

As used in the present description, the designation estradiol means 17 $\beta$ -estradiol, also designated cis-estradiol or estradiol, 1,3,5(10)-triene-3,17 $\beta$ -diol.

Polyethylene glycols (PEG's) are liquid or solid polymers of the general formula  $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$  wherein  $n$  is greater than or equal to 4. In general, each PEG is designated by a number which indicates its average molecular weight.

Starch is commonly used as an excipient in tablets. It usually functions as a binder or as a disintegrant. The present inventors believe that solving the problem of improving the bioavailability of an orally administered drug compound by including a starch in the pharmaceutical composition containing it is new and surprising.

Maize starch, potato starch, rice starch, wheat starch, and tapioca starch are examples of starches which may find use in

the present invention.

Most starches contain two different types of D-glucopyranose polymers, amylose and amylopectin. Amylose is essentially a linear polymer of  $\alpha$ -D-glucopyranosyl units linked (1 $\rightarrow$ 4).  
5 Amylopectin is a highly branched polymer of  $\alpha$ -D-glucopyranosyl units containing 1 $\rightarrow$ 4 links with 1 $\rightarrow$ 6 links at branch points. When, in the present description, starch is referred to in a generic way, it is preferred that amylose and amylopectin are also comprised by this designation.

10 Some starches for use in pharmaceutical compositions are pre-gelatinised or otherwise modified, e.g., by acid treatment, by oxidation or by hydroxyalkylation. It is preferred that such modified starches are also comprised by the designation starch when used in a generic way.

15 Cellulose, too, in various forms, is commonly used as an excipient in tablets. It usually functions as a binder, as a disintegrant or as a diluent. Cellulose can be provided in natural form as a powder or in the form of fibres, e.g., isolated from fruits or vegetables or it can be chemically modified,  
20 fied, e.g., by alkylation, hydroxyalkylation or carboxymethylation. Examples of chemically modified celluloses are methylcellulose (carmellose), ethylcellulose, carboxymethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose. The chemical modification may also  
25 comprise cross-linking. An example of this is croscarmellose. When, in the present description, cellulose is referred to in a generic way, it is preferred that all such modified celluloses are also comprised by the designation.

Further to progesterone, a PEG, an excipient selected from  
30 the group comprising a starch, a starch component, a modified starch, a cellulose, a modified cellulose, pectin, and tragacanth, and optionally estradiol, the pharmaceutical compositions according to the present invention may further com-

prise one or more of the excipients commonly used in the art such as diluents, binders, disintegrants, lubricants, buffers and preservatives. Examples of such excipients are lactose, triglycerides, polyvinylpyrrolidones, gelatine, stearic acid, magnesium stearate, silica, and talcum powder.

One of the prerequisites which must be fulfilled in order to achieve a good compliance with the prescribed regimen in self care by the patient is that the medicine must be convenient to take. Thus, if possible, tablets should only have to be taken once per day. Preferably, they should have a convenient size and they should not have a disagreeable smell or taste.

The absolute lower limit of the size of a tablet is, of course, determined by the amount of the active compound it has to contain. In practice, also a certain amount of excipients will be necessary. If a tablet is very small, it is not convenient to handle. However, a very small amount of active compound can be administered in a tablet of a convenient size by including a suitable amount of an inert diluent in the tablet formulation.

A very big tablet is not convenient to swallow, nor is it convenient to carry for example a month's supply in a hand-bag. Most conveniently, the total weight of a tablet should be from about 50 mg to about 500 mg, more preferred from about 100 mg to about 300 mg.

The kind and the amount of the excipients to be included in a pharmaceutical composition depends very much on the physico-chemical properties of the active compound to be administered and on the desired absorption profile. As already mentioned, inert excipients can be added in order to make a tablet bigger. Other excipients may be added to act as lubricants, binders, disintegrants, preservatives, in order to influence the rate of absorption or for other reasons. If a large amount of active compound is to be administered in a tablet

and large amounts of excipients are called for in order to achieve the desired pharmaceutical technical properties of the composition, it can be a problem to keep the size of the tablet small enough to be convenient. Example 4 of the present specification discloses four different tablet formulations for 100 mg progesterone tablets. Two of the formulations, A and D, have almost the same bioavailability. However, the A-tablet weighs 800 mg which makes it very inconvenient in practice, whereas the D-tablet which weighs 262.72 mg is very convenient in size.

The compositions according to the present invention are manufactured by methods known in the art. Thus, tablets or capsules comprising the composition according to the invention can, for example, be provided by:

- 15 a) mixing progesterone with a starch, a starch component, or a modified starch, adding further excipients, except lubricant, and optionally estradiol;
- b) granulating using a polyethylene glycol as a binder;
- c) optionally mixing a lubricant into the granulate;
- 20 and
- d) compressing the granulate thus obtained into tablets or or filling it into capsules.

Tablets according to the present invention may be coated or uncoated. Coated tablets may be sugar coated or film coated according to the known art.

In one preferred embodiment, the present invention relates to a composition for oral administration which comprises both progesterone and estradiol. Such a composition can be used, i.a., in the treatment of perimenopausal disorders, in the prevention or treatment of osteoporosis and in the treatment of other disorders which call for so-called opposed hormone replacement therapy.

In another preferred embodiment according to the present invention, a composition is used which contains progesterone as the sole hormone component. Such a composition may find use, i.a., as an oral contraceptive and in the treatment of disorders caused by progesterone deficiency such as certain cases of infertility, premenstrual syndrome, and dysfunctional bleeding. Further, such compositions may find use in peri-, and postmenopausal hormone replacement therapy.

The regimen for any patient to be treated with the compositions according to the present invention should be determined by those skilled in the art.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

#### EXAMPLE 1

Tablets containing 100 mg of progesterone and 1 mg of estradiol

A suitable composition for a tablet containing 100 mg of progesterone, and 1 mg of estradiol is as follows (amounts in mg):

	Progesterone	100
25	Estradiol	1
	Maize starch	50.5
	Lactose	30.5
	Polyethylene glycol 6000	33
	Croscarmellose sodium	9.2
30	Magnesium stearate	1.2
	Talcum powder	4.6
<hr/>		
	Total	230.0

Estradiol and lactose are mixed and passed through a 300 mesh screen. Progesterone, maize starch and croscarmellose sodium are added and the mixing is continued for further two minutes. Polyethylene glycol 6000 is added to the powder mixture and the granulation is performed in a high speed mixer. The granules are passed through a 2400 mesh screen and cooled in a fluid bed. After cooling, the granules are passed through an 1100 mesh screen. Talcum powder and magnesium stearate are added followed by mixing for three minutes.

10 Tablets are compressed on a rotary tabletting machine.

Tablet mass	230 mg
Tablet diameter	9 mm

Instead of maize starch, pregelatinized maize starch, potato starch, pregelatinized potato starch, rice starch, or wheat starch can be used.

## EXAMPLE 2

Tablets containing 50 mg of progesterone and 1 mg of estradiol

A suitable composition for a tablet containing 50 mg of progesterone, and 1 mg of estradiol is as follows (amounts in mg):

	Progesterone	50
	Estradiol	1
	Maize starch	31.98
25	Lactose	11.97
	Polyethylene glycol 6000	17.25
	Croscarmellose sodium	4.8
	Magnesium stearate	0.6
	Talcum powder	2.4
30	Total	120.0

The granulate is prepared as described in Example 1.

Tablets are compressed on a rotary tableting machine.

Tablet mass	120.0 mg
Tablet diameter	8 mm

5 Instead of maize starch, pregelatinized maize starch, potato starch, pregelatinized potato starch, rice starch, or wheat starch can be used.

### EXAMPLE 3

Tablets containing 100 mg of progesterone and 2 mg of estro-  
10 diol

A suitable composition for a tablet containing 100 mg of progesterone, and 2 mg of estradiol is as follows (amounts in mg):

	Progesterone	100
15	Estradiol	2
	Maize starch	50.0
	Lactose	30.0
	Polyethylene glycol 6000	33.05
	Croscarmellose sodium	9.2
20	Magnesium stearate	1.15
	Talcum powder	4.6
<hr/>		
	Total	230.0

The granulate is prepared as described in Example 1.

25 Tablets are compressed on a rotary tableting machine.

Tablet mass	230.0 mg
Tablet diameter	9 mm

Instead of maize starch, pregelatinized maize starch, potato starch, pregelatinized potato starch, rice starch, or wheat starch can be used.

#### EXAMPLE 4

##### 5 Pharmacokinetic results of the study of progesterone absorption in women

Four different tablet formulations containing 100 mg of progesterone and 2 mg of estradiol have been compared in pharmacokinetic absorption studies in healthy postmenopausal  
10 women. The composition of the tablets used are given in Table 1 and the pharmacokinetic data of the four formulations are summarized in Tabel 2.



Table 1

	Constituents per tablet	A	B	C	D
	Progesterone	100 mg	100 mg	100 mg	100 mg
5	PEG 6000		43.5 mg	21.7 mg	63.09 mg
	Kollidon k25		1.4 mg	1.4 mg	
	Kollidon va64	46.5 mg			
	Corn starch	320.0 mg	18.45 mg	18.45 mg	65.66 mg
	Stearic acid			21,7 mg	
10	Gelatine		0.5 mg	0.5 mg	0.5 mg
	Lactose	320.0 mg	18.45 mg	18.45 mg	18.45 mg
	Estradiol	2.00 mg	2.00 mg	2.00 mg	2.00 mg
	Collodial silica		2.0 mg	2.0 mg	2.63 mg
15	Croscarmel- lose sodium		9.9 mg	9.9 mg	8.48 mg
	Magnesium stearate	4.20 mg	0.98 mg	0.98 mg	1.51 mg
	Talcum powder	8.00 mg	0.4 mg	0.4 mg	0.4 mg
20	Gross weight	800 mg	197.6 mg	197.6 mg	262.72 mg

Table 2

Formulation	Number of patients	AUC Mean (nM x h)	C <sub>max</sub> Mean (nM)	T <sub>max</sub> Mean (h)
A	16	363.2	249.5	1.7
B	16	159.0	38.9	2.3
C	15	54.6	14.2	2.3
D	8	392.2	269.8	1.6

In Table 2, AUC is the area under the curve showing the plasma concentration (in nM) as a function of time (hours). C<sub>max</sub> is the maximum concentration (in nM) of progesterone in serum. T<sub>max</sub> is the time (hours) from the progesterone is administered until the maximum serum concentration is achieved.

As it appears from Table 2, the pharmacokinetic properties of the formulations A and D are very similar. However, in the case of formulation A a tablet containing 100 mg of progesterone weighs 800 mg and is thus far too big to be convenient for ordinary use. In the case of formulation D a tablet containing 100 mg of progesterone weighs 262.72 mg which is very convenient.

## CLAIMS

1. A pharmaceutical composition for oral administration which comprises micronized progesterone, a polyethylene glycol, and an excipient selected from the group comprising a starch, a starch component, a modified starch, a cellulose, a modified cellulose, pectin, and tragacanth.
2. A pharmaceutical composition according to claim 1 which further comprises estradiol.
3. A pharmaceutical composition according to claim 1 or 2 wherein the amount of progesterone is in the range of from about 10 mg to about 500 mg per dosage unit.
4. A pharmaceutical composition according to claim 2 or 3 wherein the amount of estradiol is in the range of from about 0.1 mg to about 5.0 mg per dosage unit.
5. A pharmaceutical composition according to any one of the preceding claims comprising a starch which is selected from the group comprising maize starch, potato starch, rice starch, wheat starch, and tapioca starch.
6. A pharmaceutical composition according to any one of the claims 1 to 4 comprising a starch component selected from the group comprising amylose and amylopectin.
7. A pharmaceutical composition according to any one of the claims 1 to 4 comprising a modified starch.
8. A pharmaceutical composition according to any one of the preceding claims wherein the amount of starch constitutes from about 5% to about 75%, more preferred from about 15% to about 50% by weight, most preferred from about 21% to about 30% by weight of the dosage unit.

9. A method of making a pharmaceutical composition of progesterone for oral administration having an improved bioavailability, comprising the following steps:

- 5 a) mixing micronized progesterone with an excipient selected from the group comprising a starch, a starch component, a modified starch, a cellulose, a modified cellulose, pectin, and tragacanth, adding further excipients, and optionally estradiol;
- b) granulating using a polyethylene glycol as a binder;
- 10 c) optionally mixing a lubricant into the granulate; and
- d) compressing the granulate thus obtained into tablets or filling it into capsules.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 94/00310

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/20,, A61K 9/16, A61K 31/57, A61K 47/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, MEDLINE, WPI, EPODOC

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	European journal of drug metabolism and pharmacokinetics, Volume, No 3, 1991, R. DUCLOS et al, "Comparison of oral bioavailability of two dosage-forms of progesterone in women", page 191 - page 193, figure 2 --	1-9
X	Drug Development and Industrial Pharmacy, Volume 16, No 2, 1990, R. DUCLOS et al, "Effect of ageing on progesterone-polyoxyethylene glycol 6000 dispersions" page 255 - page 265 --	1-9
X	US, A, 3862311 (L.J. LEESON), 21 January 1975 (21.01.75) --	1-9

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File WPIDS, Accession no. 86-335071, ((TEIK) TEIKOKU HORMONE MFG CO LTD) JP 61249914 A, publ. 86-11-07  --	1-9
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Information on patent family members

01/10/94

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PCT/DK 94/00310

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